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Altered reward anticipation: Potential explanation for weight gain in schizophrenia?

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Abstract

Obesity and weight gain are severe complications of mental illness, especially schizophrenia. They result from changes in lifestyle and nutrition, side effects of medication and other, less well-understood factors. Recent studies suggest that obesity and weight gain are linked to psychopathology. Specifically, severe psychopathology is associated with greater weight dysregulation, typically weight gain. However, our knowledge about the neuroscientific basis of weight gain in schizophrenia is currently limited. We propose that altered reward anticipation, which in turn is related to striatal dopaminergic dysregulation, may explain why obesity is more prevalent in individuals with mental illness. We review evidence that reward anticipation and weight change are linked by a core deficit in dopaminergic striatal circuits. Several lines of evidence, running from animal studies to preclinical and clinical studies, suggest that striatal dopaminergic neurotransmission is a major hub for the regulation of eating behavior and that dopamine links eating behavior to other motivated behavior. From this perspective, the present review outlines a unifying perspective on dopaminergic reward anticipation as a theoretical frame to link weight gain, medication effects and psychopathology. We derive important but open empirical questions and present perspectives for new therapeutic concepts.

1.1 Weight gain and schizophrenia

Schizophrenia is a brain disorder characterized by disturbances in perception, thinking, cognition, mood and volition (Kraepelin, 1915). Symptoms include hallucinations and delusions (positive symptoms), on the one hand, and diminished expression and apathy (negative symptoms), on the other. In most cases, schizophrenia begins in late adolescence or early adulthood with progressive academic, functional and social impairment following the onset of psychosis. It is a chronic condition often requiring long-term treatment with antipsychotic drugs. Interestingly, the disorder shows considerable overlap with other psychiatric conditions, in particular obesity and substance abuse disorders (Chambers et al., 2001; Crump et al., 2013). Most clinical studies largely disregard comorbidities and especially higher weight. Here, we argue that weight gain is an integral part of schizophrenia.

1.2 The clinical consequences of weight gain

Obesity is an important predisposing factor for cardiovascular disorders and metabolic disturbances, which are associated with a significantly increased risk of diabetes: The relative risk for diabetes is 2.99 in the overweight and 7.19 in the obese (Abdullah et al., 2010). As shown in a recent meta-analysis (Bak et al., 2014), the life expectancy of patients with severe mental illness is lower than that of the general population (Chang et al., 2011). Patients with schizophrenia have 2-3 times higher standard mortality ratio for all causes of death (Laursen et al., 2012). It is likely that this increased mortality is partially due to obesity as obesity is more prevalent in patients with schizophrenia than in the general population (Ratliff et al., 2013). Indeed, weight gain can be excessive (about 12 kg body weight over a course of three years; cf. Pérez-Iglesias et al., 2014a, 2014b) and is typically observed after psychotropic treatment begins, suggesting an interaction between psychiatric disease and medication.

2.1 From bench to bedside with the imaging biomarker reward anticipation

Biomarkers can form a bridge from bench to bedside in two ways: They can be correlated with disease status, expression of specific psychopathology, treatment outcome, or prediction of disease course; and they can provide insight into a mechanistic cause of disease (e.g., in longitudinal intervention studies). In the present review, we propose that impaired striatal reward anticipation signals may constitute a useful biomarker for weight gain in schizophrenia in that altered dopamine neurotransmission could be a mechanistic cause of disease. In psychiatry, it is common practice not only to assess disease status in a binary fashion (disease

present: yes/no) but to evaluate the degree of psychopathology by means of standardized observer ratings. The latter can include an assessment of the motivational deficits commonly observed in schizophrenic patients. This is an example of how biomarkers might be linked to relevant, quantitatively assessed psychopathological symptoms. These motivation deficits may not only manifest in the negative symptoms of schizophrenia but also be attributable to comorbidities. It is tempting to speculate that this may be due to a shared pathophysiological mechanism represented by a common biomarker (see Figure 2), such as impaired reward anticipation. However, the link between a core mechanism of altered reward anticipation and weight gain is not as established in schizophrenia as it is in substance use disorders or obesity. Interestingly, substance use disorder, weight gain and schizophrenia co-occur. Therefore, recent research on addiction disorders and obesity (Volkow et al., 2012) may reveal a common mechanism. Since patients with any of these conditions show decreased reward anticipation (see below), altered striatal reward anticipation may be one such mechanism. Altered striatal reward anticipation also serves as a neuroimaging biomarker for impairments in dopamine transmission.

Alternative mechanistic explanations of weight gain in schizophrenia have been proposed, focusing more on endocrine factors, histaminergic properties of medication or dysregulation of the hypothalamus (De Hert et al., 2009; Manu et al., 2015). However, this does not negate the usefulness of impaired striatal reward anticipation as a biomarker, as proposed in this review, because there is good evidence that these alternative mechanisms converge on the generation of a valence signal in the striatum (Balodis and Potenza, 2014; Heinz and Schlagenhauf, 2010; Kelley and Berridge, 2002; Rolls, 2009).

In this review, we describe obesity in patients with mental illness, and specifically schizophrenia, and the need for developing a mechanistic understanding of the links between the psychopathology of schizophrenia, antipsychotic drug treatment and weight gain. In the following, after defining and evaluating striatal reward anticipation, we discuss three questions: Is reward anticipation a valuable tool for investigating psychiatric disorders, and specifically schizophrenia? How are weight gain and obesity linked to schizophrenia? How do striatal reward anticipation and weight gain in patients converge in terms of neurological mechanisms and psychopathological phenomenology?

A neuroimaging biomarker that crosses the diagnostic boundaries between different disorders, such as addiction, obesity and schizophrenia, might be useful to a psychiatry interested in mechanistic aspects. This view is in line with the recently proposed “research domain criteria” (RDoC) initiative. The RDoC initiative defined a “positive valence” domain (Cuthbert and Insel, 2013). It was proposed that this domain defines mechanisms for characterization of anhedonia and amotivation in psychopathology which could move from DSM-IV categories to a more dimensional psychiatry (Yee et al., 2015). The constructs in the positive valence system contain approach motivation, initial responsiveness to reward attainment, sustained responsiveness to reward attainment, reward learning and habit. Approach motivation is defined by several subconstructs e.g. reward expectancy and reward prediction error (reward prediction error corresponds to the difference between received and predicted rewards). For several of these constructs, the RDoC matrix defines the monetary incentive delay (MID) task as the paradigm of choice in assessing these constructs but does not go into details e.g. how to use and operationalize the MID paradigm to quantify these subconstructs.

The vagueness of the RDoC framework regarding how one should operationalize behavioral constructs limits the capacity of translational work to bridge animal and human research, because only strictly and similarly operationalized paradigms enable comparison between species. In the following, we will outline the use of reward anticipation in different psychiatric conditions, especially obesity and schizophrenia. The reader should note that these kinds of studies rarely use standardized experimental procedures. This is especially true for studies on weight gain and eating-related behaviour. Questions such as “Does anhedonia predict weight gain?” (which has been shown in a longitudinal study of a small sample of healthy individuals; Ibrahim et al. 2016), “Is weight gain linked to therapeutic outcome?” and “Is daily dose of medication linked to treatment via an interaction with consecutive weight gain?” would be best answered using standardized procedures and while focusing on a common mechanism. Therefore, to translate between different aspects (psychopathology, motivation, comorbidities like obesity and addiction, dopamine-blocking drugs), we need a psychological mechanism with a strong neurobiological basis. By manipulating such a mechanism, we will not only learn how the different psychopathological components converge in schizophrenia and result in weight gain but maybe we will even be able to identify new treatments that also have an impact on the treatment of other disorders, such as addiction. In any case, we believe that precisely measuring reward anticipation in schizophrenia may eventually elucidate a circumscribed mechanism linking psychopathology, drug treatment effects and weight gain.

2.2 Reward anticipation

What is reward anticipation and what is its neurobiological substrate? Reward anticipation can be studied using operant conditioning. In paradigms such as the MID task, participants learn to respond to a conditioned stimulus (typically the visual presentation of a symbol on a computer screen), for example, by pushing a button (Grimm et al., 2014; Kirsch et al., 2003; Knutson et al., 2001; Plichta et al., 2012). If they give an appropriate response, they receive a reward: Rodents typically receive a food pellet and humans typically receive a symbol representing some monetary reward. The conditioned stimulus signaling the incentive and the incentive are separated in time by a short delay termed “monetary incentive delay”. Before learning, the striatum (and dopamine neurons: Schultz et al., 1997) responds to receipt of the reward; after learning, the striatum responds to the conditioned stimulus (Knutson et al., 2001).

2.3 Reward anticipation is linked to dopamine signaling

In animals, there is clear evidence that the magnitude of phasic activity induced in midbrain dopaminergic neurons by conditioned stimuli is correlated with the magnitude of reward predicted by the stimuli (Tobler et al., 2005). Similar neural responses can also be found in dopaminoceptive regions of rodents (Simpson et al., 2012) and humans (Burke & Tobler, 2011; Francois et al., 2015; Kahnt & Tobler, 2013). Behaviourally, a conditioned stimulus associated with reward often elicits a faster response than a neutral stimulus. These neural and behavioral responses to the reward-predicting stimulus reflect reward anticipation, that is, a representation of the properties of the upcoming reward, which is induced by the stimulus after but not before learning. One function of reward anticipation is to allow the organism to prepare for the receipt of reward and approach the source of reward.

When considering the neurobiological substrate of reward anticipation, we must take into account the role of the neuromodulator dopamine (DA) in the basal ganglia. There, DA is important for mediating motivation, learning and action. However, how dopamine signaling contributes to the linking of reward with motivated behavior remains poorly understood and much of our existing knowledge comes from animal studies. On the one hand, the amount of dopamine released in the striatum is taken as a proxy for the “wanting” of the reward (Berridge and Robinson, 1998). On the other hand, the phasic changes in dopaminergic signaling encode errors in reward prediction, which arise whenever the experienced reward differs from the anticipated reward

(Schultz et al., 1997). Two recent studies combine these aspects: Mesolimbic DA release is correlated with the value of work during a decision task in rats (Hamid et al., 2015) and this signal is attenuated unless a movement is correctly initiated (Syed et al., 2015). These studies demonstrate that the changes in DA release constitute both a motivational signal and a learning signal. The two aspects of DA should be kept in mind when one is comparing passive (Pavlovian) conditioning with operant conditioning because operant conditioning has an arguably stronger motivational component.

In humans, invasive studies of the role of DA are largely non-existent but have so far supported a role of DA in learning and prediction error coding (Kishida et al., 2016; Zaghloul et al., 2009). Moreover, fMRI and raclopride positron emission tomography were performed in parallel during a MID task (Schott et al., 2008). Replacement of raclopride is an indirect measure of DA release. Interestingly, DA release was found to be related to the striatal fMRI signal during reward anticipation, such that stronger cue-induced neural responses in the MID task were observed in participants with more striatal DA release during a rewarded version of the MID task. This elegant study provides one of the most convincing proofs that differences in DA release translate into differences in the blood oxygen level-dependent (BOLD) signal. Schlagenhauf et al. showed in a study with sequential not parallel DOPA-measurement via PET and consecutive MID fMRI an inverse relationship between dopamine. Other studies used pharmacological fMRI by giving indirect DA agonists and/or DA antagonists and measuring their effect on the BOLD signal (e.g., (Pessiglione et al., 2006) or raclopride PET imaging during reward anticipation and arrived at the same conclusion (cf. review by Knutson and Gibbs, 2007). Therefore, at least the striatal BOLD response measured with fMRI seems to be an adequate surrogate marker for DA-related reward anticipation, although it should be noted that the striatum receives many other inputs.

Whereas animal studies typically use primary reinforcers, such as food or liquid rewards, human studies typically use secondary reinforcers, such as money, to study reward anticipation. When comparing data obtained using these two types of reinforcers, we must consider their relationship. They could be correlated and commonalities could arise from a general reward anticipation mechanism, which is more or less the same for all kinds of valuable stimuli. Alternatively, there could be differences between reward types and even between disorders. For example, primary rewards may have more affective properties whereas secondary rewards may have more cognitive properties. Recent meta-analyses indicate that, for a broad

range of stimuli (monetary, erotic and food rewards), the ventral striatum is engaged in reward anticipation (Bartra et al., 2013; Sescousse et al., 2013). Even within individuals the striatum, as well as ventromedial prefrontal cortex, encode the value of various types of reward, for example, money and food, although reward-type-specific representations arise in other regions (Howard et al., 2015; Levy and Glimcher, 2011). However, in paradigms using primary rewards, food is typically not given directly. Instead, participants receive food points for later conversion into real food or some of the decisions made inside the scanner are realized later outside the scanner. This makes it hard to assess whether changes in reward anticipation reflect a generalized or a reward-type-specific deficit. Potential differences between primary and secondary reinforcers would be especially interesting when we study eating in the context of schizophrenia.

3.1 Reward anticipation is reduced in schizophrenia

Several lines of evidence suggest that striatal dysfunction is a core feature of the pathophysiology of schizophrenia. In humans, neuroimaging has been widely used to study brain signals related to reward anticipation. Functional MRI experiments probing reward anticipation in the ventral striatum with MID tasks reveal decreased striatal activation in drug-naïve and unmedicated schizophrenia patients (Esslinger et al., 2012; Hägele et al., 2015; Juckel et al., 2006b) as well as in participants at high clinical risk for psychosis (Juckel et al., 2012; Wotruba et al., 2014). The degree of reduced reward anticipation is linked to symptom severity (Juckel et al., 2006a; Kring and Barch, 2014; Nielsen et al., 2012) and altered dopamine activity, as suggested by the observation that treatment with atypical antipsychotics partially normalizes ventral striatal dysfunction in schizophrenia (Nielsen et al., 2012; Walter et al., 2009).

3.2 Molecular Neuroimaging of Dopamine

In this section, we describe evidence that the dopamine system is altered in schizophrenia and how functional dopamine measures and striatal BOLD fMRI signals are linked. Molecular neuroimaging studies (using PET or SPECT) have found increased striatal dopamine synthesis and dopamine release in schizophrenia, but no change in the density of presynaptic dopamine terminals (Fusar-Poli and Meyer-Lindenberg, 2013a, 2013b). Specifically, a meta-analysis (Fusar-Poli and Meyer-Lindenberg, 2013b) found a 14 % increase of striatal dopamine synthesis capacity (DSC) in 11 studies with 113 patients. Given that patients suffering from schizophrenia show a decreased reward anticipation in several fMRI studies and a decreased DSC, one would predict that higher striatal dopamine synthesis

capacity is associated with reduced reward anticipation in the same participants. In line with this prediction, healthy participants show an inverse correlation between striatal BOLD responses during reward anticipation in a MID paradigm and striatal dopamine synthesis capacity as measured with DOPA labeling (Schlagenhauf et al., 2012). However, healthy participants also show a positive correlation between increased dopamine release as measured by raclopride displacement and striatal BOLD reward anticipation signals in a variant of the MID task (Schott et al., 2008).

To reconcile these seemingly contradictory findings in healthy participants, we need to look in more detail at the different functional measures of dopamine and how the striatal BOLD response may be related to them. Schlagenhauf and colleagues (2012) measured dopamine synthesis capacity, which is more closely related to tonic dopamine release than the shorter-lived dopamine release measures of Schott and colleagues (2008). While Schott et al. might have measured the faster phasic response, the DSC in Schlagenhauf et al.'s study is more related to the tonic dopamine release. Tonic dopamine seems to be negatively correlated with the fMRI striatal signal (representing phasic dopamine). In line with this notion, the animal literature proposed that slow background (i.e., tonic) and fast stimulus-evoked (i.e., phasic) dopamine release are negatively related (Goto et al., 2007). By extension, striatal BOLD would pick up primarily phasic dopamine release induced by reward-associate stimuli (like in MID paradigms). Lower reward anticipation signals measured with fMRI might, therefore, arise either from a lower phasic response or from an increased (or altered) tonic dopamine level.

Tonic dopamine levels modulate the intensity of the phasic dopamine response (Grace, 1991) and are regulated primarily by presynaptic D2 autoreceptors (Ford, 2014). It is likely that dopamine synthesis capacity as indexed by DOPA is regulated by presynaptic autoreceptors. Accordingly, Schlagenhauf and colleagues (2012) propose that the negative correlation between striatal dopamine synthesis capacity and prediction error-related activity may reflect the homeostatic role of autoreceptors. In contrast, raclopride-displacement as used by Schott and colleagues primarily reflects postsynaptic effects of dopamine release, implying a positive monotonic relation between striatal fMRI and raclopride-displacement.

While molecular neuroimaging in humans can provide a missing link between less invasive human fMRI studies and more invasive studies in animals, it should be kept in mind that the temporal resolution of molecular imaging methods is very low and based on a much smaller number of patients than fMRI MID findings. Invasive animal research comes with higher temporal resolution and can clarify the link

between reward anticipation and dopamine release. Indeed, in rats, optogenetic stimulation of dopamine neurons in the midbrain increases striatal BOLD responses (Ferenczi et al., 2016; Lohani et al., 2016), and this increase is blocked by dopamine receptor antagonists (Ferenczi et al., 2016). Moreover, a translational study using an MID-like paradigm (Francois et al., 2015) showed that a conditioned stimulus elicits a surge in dopamine release in rats. Thus, both striatal dopamine (measured with voltammetry in rats) and striatal BOLD (measured with fMRI in humans) show a burst of activity at the presentation of a reward predicting conditioned stimulus. Together, these findings corroborate the notion that striatal activation in humans can reflect phasic dopamine release.

In conclusion, reward anticipation, as measured by BOLD fMRI, appears to be closely related to striatal dopaminergic neurotransmission, although it should not be forgotten that the striatum receives many other inputs. Moreover, the fact that lower reward anticipation signals measured with fMRI can from multiple changes in dopamine function might explain why studies on disorders other than schizophrenia, such as obesity, ADHD, or depression can commonly report decreased striatal fMRI response.

3.3 Reward anticipation is a valid endophenotype in schizophrenia

As schizophrenia and obesity are disorders with a relatively strong genetic background, it might be useful to identify biomarkers that bridge the gap between genetic association studies and neural mechanisms in small clinical neuroimaging studies. A phenotype that can be objectively measured and that is found in genetically predisposed individuals is called an endophenotype. It is a theoretically well-founded assumption that these endophenotypes not only show larger effect sizes, but are more closely linked to true neurobiological mechanisms (Gottesman and Gould, 2003; Meyer-Lindenberg, 2010). There is good evidence that this is true for reward anticipation: Recent research has established reward anticipation as an intermediate phenotype, a genetically wired phenotypical expression of a neural mechanism (Grimm et al., 2014). A genetic base for increased dopamine synthesis in the striatum was found via molecular neuroimaging in healthy first-degree relatives of schizophrenia patients. The relatives showed the same pattern as patients with schizophrenia (Huttunen et al., 2008). A recent study investigating neural reward anticipation responses with fMRI in healthy first-degree relatives of schizophrenia patients and comparing them to the responses of healthy matched controls without genetic liability for psychosis came to the same conclusion (Grimm et al., 2014). These findings lead to the question why weight gain does not start earlier given that the striatal dysfunction is in fact present before the onset of psychosis. We will discuss this question in the following.

3.4 Reward anticipation is a transdiagnostic feature in psychiatric disorders

MID paradigms are not used exclusively in schizophrenia research. While a discussion of all aspects of reward anticipation in psychiatric disorders is beyond the scope of this review, we would like to mention the possibility of a transdiagnostic perspective. Such a perspective could suggest a common pathophysiologic mechanism for related and often co-occurring psychiatric disorders. One example of a transdiagnostic perspective comes from a recent study by Hägele and colleagues (2015) which used the same MID task in patients with schizophrenia, major depression, alcohol addiction, bipolar manic episode, or ADHD and found commonly reduced reward anticipation signals in schizophrenia, major depression and alcohol addiction.

4 Obesity-related changes in striatal reward processing

So far, we have seen that weight gain and schizophrenia might be linked by striatal dysfunction. If we suspect that there is a specific mechanism (namely, striatal reward anticipation related to phasic dopamine responses) in schizophrenia that mediates weight gain, we might ask whether such a mechanism is found in otherwise healthy obese patients. We will develop the argument by discussing the relevance of reward in obesity in general and then reward anticipation and its relation to food-cue-induced activation of the striatum and other reward-related brain areas.

First, in humans, dopaminergic neurotransmission is related to obesity. This has been shown in PET studies investigating the binding of radioligands to the D2 receptor. A reduction in striatal dopamine-2 receptors was found in pathologically obese participants (Wang et al., 2001). This led to the hypothesis that obesity shares some neurobiological mechanisms with addiction disorders, for example, and mainly, the need to compensate for a decreased sensitivity of dopamine D2-regulated reward circuits by impulsive eating (Stice et al., 2008; Wang et al., 2004). While this provides us with good evidence that the dopaminergic reward system is involved, it gives us no information about reward anticipation in MID paradigms.

Second, in MID paradigms – presumably reflecting phasic dopaminergic responses – reward anticipation differs in obese or binge-eating patients on the one hand and healthy non-obese controls on the other (Balodis et al., 2013; E. Stice et al., 2008; Stoeckel et al., 2008). However, an apparent conundrum is the direction in which the striatal fMRI signal changes. While the reviewed studies show a blunted striatal response in patients with schizophrenia (or depression) and their relatives, the picture is less clear in obesity.

As explained above, while we propose to explain obesity in schizophrenia as resulting from a decreased striatal signal during reward anticipation, some obesity studies point to enhanced cue reactivity (Pursey et al., 2014), possibly reflecting a distinct pathway to obesity. However, the striking differences in the various paradigms, populations, and methods used to study obesity make it hard to generalize across studies. Most studies of cue processing presented images of appetizing food stimuli to obese patients. These studies found an increase in striatal reactivity when participants viewed these stimuli (Pursey et al., 2014). It is hard to relate these studies to studies using MID tasks due to several methodological issues: monetary (MID) vs. food rewards, event-related (MID) vs. block designs, uncontrolled satiation status (MID) vs. fasting or satiated participants, operant (MID) vs. Pavlovian conditioning, images often not controlled for calorie content etc. While keeping this in mind, the presentation of an appetizing cue to an obese participant might nevertheless share some characteristics with the presentation of a conditioned stimulus that potentially predicts the delivery of a monetary reward.

While the insightful studies by Eric Stice using primary rewards in Pavlovian designs (Burger and Stice, 2012; Stice et al., 2009, 2010a) suffer from the aforementioned issues, they nevertheless provide important leads on how primary rewards given directly in the scanner can pave the way for studying striatal food reward anticipation. In overweight adolescents, Stice and colleagues observed overactivation in the striatum as well as in OFC, insula, and opercular regions during anticipation of a food reward (Stice et al., 2008). This altered response in individuals who were at risk for obesity was identified as an imaging biomarker for obesity risk.

The link between obesity and food anticipation is not limited to an arbitrary threshold (obesity defined as > 30 kg/m^2) for obesity. Instead, body mass index (BMI) relates to striatal activation in a gradual fashion. During food receipt, there is an inverse correlation between BMI and striatal activation: Higher BMI is associated with a decreased BOLD response (Stice et al., 2010a, 2010b, 2011a). Decreased activation of the striatum in response to the imagined intake of palatable foods has also been associated with weight gain at a 6-month follow-up (Stice et al., 2010a). This is an important finding because it shows that an fMRI-derived neuroimaging biomarker closely related to striatal reward anticipation can predict a clinical outcome, in this case, weight gain. Studies in psychiatric patients might additionally try to relate this to specific psychopathology.

Third, on the one hand, dopaminergic dysregulation leads to obesity but, on the other hand, chronic changes in eating behavior result in changes in striatal reward processing and might have an impact on dopamine function in the striatal reward system. For example, a chronically high-fat, high-sugar diet can lead to a down-regulation of D2 receptors in animals, mimicking the neural response to the chronic use of drugs that increase dopamine signaling (Alsiö et al., 2010; Lockie et al., 2015; Val-Laillet et al., 2015). This biologically strong effect has not been systematically studied in humans and its relation to reward anticipation remains unclear but it suggests that longitudinal neuroimaging studies of reward anticipation during altered food intake might reveal comparable phenomena in humans.

Fourth, obesity is not caused by a single behavior, for example, overeating (Elman et al., 2006; Stice et al., 2011b; Ziauddeen et al., 2015), but falls into different behavioral categories. One example comes from binge-eating disorder with and without obesity. In a small study, patients with binge eating disorder showed decreased striatal reward anticipation as compared to patients with obesity (Balodis and Potenza, 2014). Conversely, obese participants showed increased bilateral ventral striatum recruitment as compared to lean participants.

In summary, studies on monetary incentive delay in people with obesity appear to be missing. Such studies would enable us to elucidate the mechanisms underlying weight gain in schizophrenia. Either weight gain in obesity shows the same behavioral pattern (of being related to decreased reward anticipation) or obesity in schizophrenia and obesity in mentally healthy patients fall into two different categories. We identify studies on MID in people with obesity as a missing link for relating weight gain in psychotic and non-psychotic patients. In addition, studies with standardized cue-presenting paradigms (food stimuli and/or food receipt) might provide us with another missing link in the other direction: While numerous cue-reactivity studies have been conducted in people with obesity, there is only a single food cue-presenting study in people with schizophrenia (Grimm et al., 20 12).

A last, delicate, point is the development of reward anticipation over time. The reduced levels of D2 receptors in patients with obesity do not simply translate into the reduced reward anticipation signals observed in fMRI studies. Some studies found a hyperreactive reward system, while others found hyporeactivity in obese patients during the presentation of appetizing cues (DelParigi et al., 2004; Matsuda et al., 1999; Rothemund

et al., 2007; Volkow et al., 2008). Val-Laillet and colleagues (2015) proposed a way to reconcile these findings. Hyperresponsivity of the reward circuitry may occur primarily in early stages of obesity, at least in individuals who are genetically predisposed to a higher dopamine signaling capacity. Thus, hyperresponsivity to stimuli predictive of food reward may be one factor leading to increased food intake. By contrast, hyporesponsivity of the reward circuitry may be associated with attempts to compensate and with further weight gain at more advanced stages of obesity. Accordingly, overeating may decrease the responsivity of the reward system, which in turn could lead to compensatory eating.

However, studies with a strict longitudinal setup of MID in obesity are missing. Stice and colleagues (Stice et al., 2010a) were able to predict future weight gain by a weaker striatal activation. Yet, their "milkshake"-paradigm was not a MID tasks making comparability difficult with the more standardized reward anticipation in MID discussed here.

While obesity might be characterized by enhanced anticipation for both food and monetary rewards, schizophrenia might be associated with decreased reward anticipation. In this case, the mechanisms of how dopaminergic reward anticipation leads to weight gain would be different in obesity and schizophrenia. Our review suggests that this is unlikely, but points to a gap in available data bridging obesity and schizophrenia using comparable paradigms. A study comparing obese and schizophrenic patients with the same paradigm (e.g. MID-task) would empirically assess the possibility of a common pathomechanism. In addition, behavioral aspects may go beyond disease categories. For example, eating behavior may be more closely related to reward anticipation than to disease category, with sporadic overeating linked to decreased reward anticipation and chronic overeating linked to enhanced cue reactivity. In summary, further research should compare obesity and schizophrenia, use standardized MID-tasks and assess disease-independent eating behavior.

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Figure 1 Hypothesized dopaminergic dysregulation and weight in the course of schizophrenia. The y-axis gives the implied relation in comparison to the population average, the x-axis shows the different stages of the disease, illustrating, for example, the relation between weight gain and a blunted dopamine signal in the chronic phase. The "dopamine"-line is a hypothetical value for a phasic-to-tonic-dopamine signal (with fmri reward anticipation providing a proxy). Anti-DA refers to antidopaminergic medication aka antipsychotics. Please note the speculative nature of the scheme, which illustrates our argument but is only partly based on empirical data. Numbers with black background point to the reference proving the specific point: 1) genetic basis of low reward anticipation (Grimm et al., 2014) **2) acute psychosis comes with a dysregulated dopaminergic regulation converging to illicit salience attribution of stimuli** (Howes et al., 2009; Howes and Kapur, 2009) **3.) antidopaminergic medication suppresses**

reward anticipation and initiates weight gain (Juckel et al., 2006a; Nielsen et al., 2016) **4.) antipsychotic therapy can induce normalization of reward signaling while weight plateaus** (Nielsen et al., 2012; Pérez-Iglesias et al., 2014)

5.1 Role of medication in weight gain

Pharmacological treatment of schizophrenia involves antipsychotics, a diverse class of drugs, which share their antagonistic action on the D2 receptor and which presumably result in blocked phasic dopamine effects in the striatum and elsewhere in the brain. A recent meta-analysis showed that all antipsychotic drugs are associated with weight gain (Bak et al., 2014). Moreover, antipsychotic medication is not only related to weight gain in schizophrenia but also in other severe mental disorders (Bak, Fransen, Janssen, van Os, & Drukker, 2014; Parsons et al., 2009; Rummel-Kluge et al., 2010). In the following, we will review evidence for a common pharmacological mechanism and a relation to reward anticipation.

First, we investigated whether the medication-related weight gain arises from higher energy intake or from lower energy expenditure. This is interesting from a neurobiological and a clinical level because tonic levels of dopamine are important for movement initiation. However, studies in patients are inconclusive. While the atypical dopamine antagonist olanzapine led to increased energy intake in patients with schizophrenia (Gothelf et al., 2002), this was not the case for haloperidol. Neither drug changed resting-state energy expenditure. In schizophrenia patients treated with clozapine, energy expenditure was decreased (Sharpe et al., 2006). While this is a clinically valid cohort, it is not clear whether the reduced energy expenditure stemmed from the medication or from the illness. In summary, there seem to be two behavioral aspects: one leading to a decrease in motivation to move and one leading to an increase in motivation to ingest high-caloric diets (without strong effort exertion for gaining this additional energy).

Although overeating is not easy to induce in other organisms besides humans, animal studies provide converging evidence for a role of at least some antipsychotics in increased energy intake. Specifically, in a study in female rats, sub-chronic olanzapine led to an increase in meal size and in overeating (Davoodi et al., 2009). These studies suggest that antipsychotics result in increased energy intake, while further research is necessary to determine the effect of antipsychotics on energy expenditure.

In everyday clinical practice, medication-related weight gain seems to depend on several factors, including treatment length, type of antipsychotic, and baseline weight (whereby leaner patients gain more weight). The weight gain seen with drugs like olanzapine and clozapine can be substantial, although it should be noted

that especially clozapine is a drug used for the treatment of treatment-resistant patients (Kane & Correll, 2016), thereby confounding drug-induced weight gain and severity of illness. Weight gain appears to be greatest and most rapid during the first 6 weeks of treatment (Ascher-Svanum et al., 2005; Kemp et al., 2013), with a trend toward a plateau after 12-18 months of treatment (Perez-Iglesias et al., 2008; Pérez-Iglesias et al., 2014).

While the amount of weight gain resulting from different antipsychotics may vary, when looking for a common mechanism, we need to consider which specific pharmacological properties olanzapine or clozapine have that ziprasidone or aripiprazole do not (these specific properties are documented in a meta-analysis of head-to-head trials by Rummel-Kluge et al., 2010). One candidate mechanism of increased weight gain is the antihistaminergic property of both olanzapine and clozapine (Deng, Weston-Green, & Huang, 2010). By blocking the histamine H1 and H3 receptors, these drugs may weaken a histamine-mediated satiety signal in the hypothalamus where histamine contributes to satiety and hunger signaling (Ishizuka et al., 2006). Therefore, compared to drugs with histamine action, treatment with antipsychotic drugs without direct involvement of histamine receptors may result in less weight gain.

However, histaminergic action cannot fully explain the subsequently increased weight gain: As a recent meta-analysis pointed out, all antipsychotic drugs result in weight gain (Bak et al., 2014). While the antihistaminergic properties might explain why some drugs result in faster or greater weight gain, they do not explain the mechanism common to almost all antipsychotics. In this context, it is interesting to look at one of the rare longitudinal clinical studies that evaluated weight gain over the course of more than 12 months. This Spanish study compared weight gain resulting from treatment with risperidone, haloperidol and olanzapine. In the first three months, olanzapine resulted in faster weight gain than risperidone or haloperidol, but after over 12 months, the amount of weight gain resulting from treatment with these drugs (8-10 kg) was not significantly different (Perez-Iglesias et al., 2008; Pérez-Iglesias et al., 2014). These data suggest that there is a shared general mechanism of weight gain induced by antipsychotics. In line with this finding, a Cochrane review in 2010 did not see convincing evidence for antipsychotic switching strategies to prevent weight gain (Mukundan et al., 2010): The authors suggested that switching antipsychotics would not lead to clinically significant differences in weight gain, probably because the differences between drugs are smaller than the general drug effect.

Next, to elucidate the general effect of antipsychotics on weight gain, we will consider treatment efficacy and the pharmacological mechanism of antipsychotics. So far, most reviews discuss weight gain as a side effect that is independent of treatment efficiency and not linked to the pharmacological mechanism. The pharmacological mechanism of antipsychotics is far from clear, but a consensus view is that all antipsychotics modulate striatal dopamine neurotransmission. In almost all drugs, this is done by blocking the dopamine D2 receptor (Kapur, 2000). The degree of D2 blocking is related to the clinical efficacy of the antipsychotic. Thus, the question arises whether clinical efficacy is related to weight gain.

A meta-analysis of head-to-head randomized trials seems to suggest that the most effective drugs indeed show the strongest weight gain, although the authors did not systematically assess the relation (Rummel-Kluge et al., 2010). In line with this notion, previous studies indicated that weight gain and improving psychopathology during clozapine treatment are linked (Meltzer, Perry, & Jayathilake, 2003). On the other hand, a small trial with *N*=181 patients suggested that treatment success is associated with weight gain only in the case of olanzapine, but not other antipsychotics (Czobor et al., 2002). Possible reasons for the inconsistent results include failure to adjust for initial body weight and level of psychopathology, differences in trial duration, previous outcome measures, the reliability of assessment, concomitant medications, and clozapine dosage.

Sharma and colleagues (Sharma, Rao, & Venkatasubramanian, 2014) reviewed 15 studies investigating the relation between weight gain and antipsychotic treatment and discussed whether a “metabolic threshold” exists for olanzapine or clozapine. They indeed found some indication that olanzapine or clozapine do not work as efficiently when they do not have an impact on weight. This weight effect can be conceptualized as a “metabolic threshold”. However, they point out that data for other drugs are sparse or even non-existent, that only the large, naturalistic CATIE trial reported that weight gain after 18 months was significantly associated with psychopathology and that no differences with respect to weight gain were found between the drugs used in the trial (perphenazine, olanzapine, risperidone, quetiapine and ziprasidone; cf. Hermes et al., 2011). Therefore, it would be promising to test the hypothesis that the decisive feature of the general medication effect is not a particular pharmacodynamic property of the specific drug, but an unspecific switch or modification in the dopaminergic striatal reward system. If this hypothesis is confirmed, it would explain i)

why a drug's specific pharmacology is not as decisive because these drugs modulate striatal dopamine processing (Howes & Kapur, 2009; Kapur, 2000) and ii) why patients who are genetically prone to a blunted reward response are in the long run especially prone to developing weight abnormalities when treated with antipsychotics. We, therefore, propose that dopamine-based reward anticipation is a mechanism that could underlie the general effect of antipsychotics on weight gain.

The only longitudinal study in this area used a MID paradigm to study weight change in patients treated with the highly selective D2- and D3-receptor antagonist amisulpride (Nielsen, Rostrup, Wulff, Glenthøj, & Ebdrup, 2016). Confirming our proposal, a decrease in reward anticipation over the course of 6 weeks predicted greater weight gain. This supports the previous suggestion that antihistaminergic mechanisms cannot be the sole mechanism underlying weight gain: Amisulpride does not result in histaminergic action.

The longitudinal MID study should be replicated and complemented by studies of other antipsychotics because open questions remain. For example, is D2 blockade a necessary feature of drugs modulating reward anticipation (and therefore food intake and energy expenditure)? Data from bipolar disorder and depression suggest that antidepressants and phase-prophylactic drugs like lithium can also result in a substantial increase in weight. Tricyclic antidepressants induce a dose-dependent continuous weight gain of 0.57 to 1.37 kg per month of treatment. Lithium maintenance therapy stimulates weight gains of over 10 kg in 20% of patients (Garland, Remick, & Zis, 1988). While these findings point towards additional mechanisms, it remains an open question whether all drugs resulting in weight gain involve a final common pathway in the form of dopaminergic transmission in the striatum.

5.2 Why does weight gain not start before pharmaceutical treatment?

Previous cross-sectional studies have found that reduced reward anticipation is linked to weight gain, obesity, schizophrenia or psychopathological measures like anhedonia. Does reduced reward anticipation also predict within-subject weight gain over time? Only one recent longitudinal study looked at the relation between weight gain, striatal activity and antipsychotic treatment in schizophrenia. At follow-up, six weeks after baseline measurement with amisulpride, Nielsen and colleagues (Nielsen et al., 2016) found in *N*=39 patients treated with amisulpride that reward anticipatory responses in the MID task were associated with weight gain. Patients with lower baseline reward anticipation in the right putamen showed stronger weight

gain. In the follow-up measurement, weight gain was associated with an increase in putamen activation during treatment. While this fits well with the concept of a blunted striatal reward anticipation being related to weight gain, the editorial (Kapur and Marques, n.d.) asked why patients did not put on weight long before pharmaceutical treatment took place. Is amisulpride the causal agent or just a trigger in an already dysregulated striatal reward system? In other words, given that dopaminergic dysregulation already takes place in drug-naïve patients, to what degree is weight dysregulation independent of medication?

Several observations suggest that medication is not the only factor contributing to weight gain in schizophrenia: Disruptions of glucose regulation have been observed in medication-free patients (Ryan et al., 2003; Spelman et al., 2007); this mirrors classical descriptions by Emil Kraepelin of weight loss in acute psychosis and weight increase in the long run (Kraepelin, 1919). A small, but technically sophisticated study found that medication-naïve patients with schizophrenia have more visceral fat as measured by CT (Thakore et al., 2002). This is also relevant from an epidemiological standpoint because of the strong health implications of visceral fat, namely, that it is associated with a disadvantageous lipid profile and – according to the INTERHEART study – with a higher risk of heart infarction (Yusuf et al., 2004).

Interestingly, the link between schizophrenia and obesity exists on a genetic level as well. Unaffected first-degree relatives of patients with schizophrenia share psychosis-disposing gene sets with their affected siblings and also have higher rates of diabetes (19–30%, compared to 1.2–6.3% in the general population) (Mukherjee et al., 1989). This not only works in the direction of schizophrenia genes predisposing to metabolic syndrome but also vice versa: In a genome-wide association study of obesity, risk genes were significantly associated with schizophrenia in a Danish sample and its replication cohort (Hansen et al., 2011). These findings underscore the possibility that an already existing dysregulation in striatal neurotransmission predisposes to weight change, which is further modulated by antipsychotics, and results in an increase in weight. In other words, while the onset of weight gain is tightly linked to medication, patients with schizophrenia are a high-risk population for weight gain. In this view, vulnerability is conveyed genetically and through a sensitive, easily dysregulated striatal reward system. Empirical corroboration can only be provided by longitudinal studies with a timeline long enough to capture enough variance in weight.

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Figure 2 Striatal dysregulation as core overlap between the psychiatric comorbidities of schizophrenia, obesity, depression and addiction

6. Dopamine modulates energy homeostasis and thriftiness

While dopamine is commonly discussed in terms of motivation, reward impulsivity, incentive salience and reward prediction learning (Berridge, 2012; Schultz, 2012), its role in the regulation of energy expenditure is often neglected. From a broader perspective, the role of dopamine in behavioral flexibility and instrumental learning is consistent with the view that dopamine regulates thrift, that is, the degree to which an animal exploits its prior reward learning to maximize return on energy expenditure (Beeler, 2012). In this view, dopamine provides a balance between exploration and exploitation of an energy source. This role has implications for two fundamental decisions concerning weight gain: how much energy does the organism have to expend to obtain energy from current/known vs. future/unknown food sources? and how thrifty does it need to be in using available energy? This balance between energy-costly exploration and energy-preserving exploitation is an energy-related thriftiness, possibly associated with dopamine levels (different aspects of high vs. low thriftiness are explored in Table 1). In this view, low levels of dopamine action, associated for example with schizophrenia and antipsychotics, will result in increased exploitation whereas high levels of dopamine action will result in increased exploration.

When considering whether to use energy and explore or conserve energy and exploit, environmental characteristics also play a role. We can distinguish between energy-rich and energy-poor environments based on the availability and quality of rewards. In an energy-poor environment, it may be more adaptive for the organism to exploit prior experience to increase thriftiness and maximize return on expenditure. This is true for starving elephants that typically return to the same waterhole and it is true for a patient with schizophrenia who suffers from negative symptoms and returns to the refrigerator stuffed with energy-rich rewarding stimuli. While this is a functional behavior for a starving organism in an energy-poor environment, it is dysfunctional for a patient living in an energy-rich environment. By contrast, in a high-energy, high-reward environment, the organism can expend much more time and energy exploring and potentially find even better rewards.

A sudden increase in phasic dopamine via stimulant intake, for example, would elicit a different behavior (in contrast to D2-receptor blocking antipsychotics), namely, manic-like behavior with an increase in exploratory behavior. Such an increase in phasic dopamine would be mirrored by a change in striatal activity during reward anticipation. Weight loss during stimulant intake, psychotic or manic behavior is common in clinical settings, but may be less pronounced since access to high-energy food is easy in modern society. In any case, the interaction between internal (phasic dopamine) and external (energy density of the environment) variables provides a new perspective on weight regulation in schizophrenia. From this perspective, psychopathology and medication in schizophrenia affect food foraging behavior and energy intake. Chronic illness and the down-regulation by antipsychotics lead to an increase in thrift: The organism starts exploiting available energy resources by eating the highly available energy-rich food. Over the course of several months of antipsychotic treatment, one cannot have antipsychotic effects without a change in eating behavior because dopamine is a regulator of energy homeostasis.

In summary, under the assumption that dopamine is involved in the organism's energy allocation, schizophrenia may be related to dysregulated energy allocation. The dopaminergic mechanism of energy allocation appears to be evolutionarily preserved and found even in model organisms like Caenorhabditis elegans (Calhoun et al., 2015). Recent studies implicate dopamine in a final common pathway that couples energy sensing with regulated voluntary energy expenditure (Beeler et al., 2012, 2010). Therefore, phasic dopamine and its BOLD-response equivalent of striatal reward anticipation could be viewed not only as a learning signal but as a mechanism linking food reward expectations and consumption with energy expenditure. In line with this view, a recent study suggests that dopamine signals represent the amount of work needed for navigating, exploring and exploiting the environment (Hamid et al., 2015). This provides a bridge to understanding schizophrenia as a disorder that leads to misaligned striatal reward-anticipation signals and a distorted perception of the environment. In this view, positive symptoms such as delusions and hallucinations go together with active, exploratory but in the long-run unsuccessful behavior. By contrast, the chronic and negative symptoms are characterized by an increase in energy intake (=higher exploitation) and less exploratory behavior (=amotivation). This effect is further amplified by therapy with antidopaminergic medications.

Thrift	Increase	Decrease
Environment	Energy-poor	Energy-rich
Exploitation	Increase (e.g. plundering the refrigerator)	Decrease (e.g. because of a work-related deadline, one ignores one's favorite pizza restaurant)
Energy expenditure	Decrease (e.g. sleeping in front of the TV)	Increase (e.g. playing football with friends)
Exploratory behavior	Decrease (e.g. loss of interest, anhedonia, loss of social contacts)	Increase (e.g. more social activity, applying for a job)
Phasic / Tonic dopamine	Decrease	Increase
fMRI striatal reward anticipation	Decrease	Increase
Drugs	D2-blocking antipsychotics	Direct and indirect dopamine agonists (e.g. methylphenidate)
Mental illness	Chronic schizophrenia, negative symptoms	Acute mania, drug-induced psychosis, acute schizophrenic psychosis

Table 1. Thrift as a dopaminergically mediated behavior that regulates the balance between energy expenditure and consumption.

7. Outlook: possible new therapies for comorbid obesity

There are several good reviews on specific aspects of weight gain in schizophrenia. They typically concentrate on i) dysregulation of neuroendocrinological circuits (e.g., hormonal regulation by the hypothalamus; Sharma et al., 2014); ii) dysregulation of peripheral hormones (e.g., leptin and ghrelin) implicated in weight homeostasis and in regulation of glucose (De Hert et al., 2009; Mitchell et al., 2013; Sentissi et al., 2008); and iii) the effect of antipsychotic medication on weight (Bak et al., 2014; Deng et al., 2010; Sharma et al., 2014). All of these factors are important. Nevertheless, we propose an additional factor, namely, that a dysregulation of striatal dopaminergic mechanisms (Fusar-Poli and Meyer-Lindenberg, 2013b;

Winton-Brown et al., 2014) can result in weight gain. We believe that the link between weight gain and schizophrenia can provide a great deal of pathophysiological insight. Although medication seems to play an important role, there is evidence that patients are predisposed to weight gain and therefore constitute a population which is more vulnerable to the effects of medication. Can this perspective help us generate new ideas about how to treat obese patients?

Although common-sense advice ("move a little more, eat a little less") may sound like an easy and effective strategy, many of the core psychopathological symptoms of patients with schizophrenia, such as depressed mood, amotivation, disorganized thinking, cognitive dysfunction etc., result in their not following such advice. Through improved understanding of how thinking, mood and weight gain are linked on the neural level and interact with environmental variables, we may navigate a precisely mapped mechanism and pave the way for innovative treatment and diagnostics. According to this approach, dopamine is an important modulator of the energy allocation linked to explorative behavior. Consequently, we would expect that a range of therapeutic options from fitness training (explorative behavior becomes more efficient and less energy consuming), to microbiome treatment (change of energy intake and metabolisms has an impact on dopamine) or chronobiological interventions (adjusting day/night cycle to actual day-night phases) may have a positive effect on energy allocation behavior and on dopamine signaling. More generally, we hope to stimulate a translational perspective, which views eating behavior and weight issues as a product of behavior. Accordingly, we believe that dysregulated dopaminergic reward anticipation provides a framework that informs and inspires innovative new as well as existing therapies.

We hope that future research will address the most pressing questions, such as how the treatment of obese and non-obese patients with schizophrenia should differ and whether the treatment of obesity that co-occurs with psychopathology should differ from that of obesity independent of psychopathology. These studies should enable direct comparisons of patients with schizophrenia and weight-matched obese controls. For example, following Nielsen and colleagues (Nielsen et al., 2016), we should try to study the predictive ability of striatal reward anticipation in patients with respect to weight gain, psychopathology and comorbid disorders over longer terms (6-18 months). Shorter-term studies would result in less variance and weight gain would plateau after about 12 months (Perez-Iglesias et al., 2008). The longer-term perspective may help us prevent comorbidities in our patients and design new and efficient treatments. A speculative synthesis of the long-

term relation between weight and dopaminergic dysregulation during the course of schizophrenia is plotted in Figure 1. In this view, weight corresponds to the sum of the dopaminergic (dys-)function.

Due to the previously discussed role of dopamine as a modulator of energy allocation in terms of energy intake and energy spent for reaching food resources, the most obvious therapeutic application would be to increase energy expenditure by sports activities. This should favorably affect striatal dopamine levels. Indeed, greater motor activity is linked to an increase in dopaminergic signaling (Cachope and Cheer, 2014; Fazio et al., 2011). Mechanistically, acute physical exercise activates the dopaminergic reward pathway through increases in dopamine concentrations and dopamine receptor binding (Greenwood et al., 2011). Moreover, chronic voluntary and forced running increases dopamine levels in the brain (Foley and Fleshner, 2008; Greenwood et al., 2011; Sutoo and Akiyama, 1996). The ventral tegmental area shows stronger phasic dopamine spikes after voluntary wheel running in rats (Wang and Tsien, 2011), suggesting that neurons in the ventral tegmental area code motivational signals which trigger, sustain, or end movement. Animals that are bred for increased wheel-running have higher dopamine concentrations in the ventral striatum as measured by chromatography (Mathes et al., 2010). This makes physical exercise therapy very promising from a neurobiological point of view.

from a neurobiological point of view, these rodent findings suggest that physical exercise therapy could be a promising treatment for both obesity and reduced dopamine levels.

While one recent meta-analysis on humans supports exercise as “a robust add-on treatment” (Dauwan et al., 2015) in schizophrenia, its efficacy is often hard to establish in clinical reality. Indeed, a different meta-analysis of n=94 schizophrenic patients did not support the hypothesis that physical exercise leads to clinically relevant weight loss in schizophrenia (Krogh et al., 2014). The authors therefore question whether a simple exercise program translates to clinical effects, a conclusion mirrored by studies on the effects of exercise in depression. It is conceivable that combining increased exercise with changes in diet might lead to stronger effects. In any case, it would be interesting to study biomarkers and dopaminergic signaling before and after such an intervention training.

Still, these intervention concepts are obviously highly simplistic. More movement and less intake are easier said than done. We need more elaborate techniques which target everyday behavior effectively and in a relatively automatic manner. While such a program might work more easily in an inpatient setting, translation into the everyday life of patients will be even harder to achieve. When patients show amotivation, it is difficult

to motivate patients, and this difficulty also extends to participation in sports activities in their real life. The use of behavioral therapy could be enhanced by devices that provide immediate and long-term feedback on behavior and health measures. At least younger patients will have fewer problems adapting to new mobile health-monitoring possibilities ranging from smartphone applications to wristbands.

These devices will be able to measure a proxy of energy expenditure (e.g., movement), give feedback in relation to targets and elicit self-ratings of psychopathology. Such an approach would not only provide interesting new real-life datasets, but also facilitate motivation through “gamification” (Yang et al., 2015) of healthy behavior. Related approaches have been taken for HIV care or patients suffering from chronic rheumatoid arthritis (Allam et al., 2015).

Apart from these conceptual examples, clinical studies that measure neuroimaging biomarkers for dopaminergic mechanisms will have to verify the ideas outlined in this perspective article. In any case, given the current state of the art, we believe that a unifying perspective on dopaminergic reward anticipation not only provides us with the theoretical framework to link weight gain, medication effects and psychopathology but also has the potential to deliver fresh insights as well as new and promising therapeutic concepts to counteract weight gain in schizophrenia.

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Figure 1.

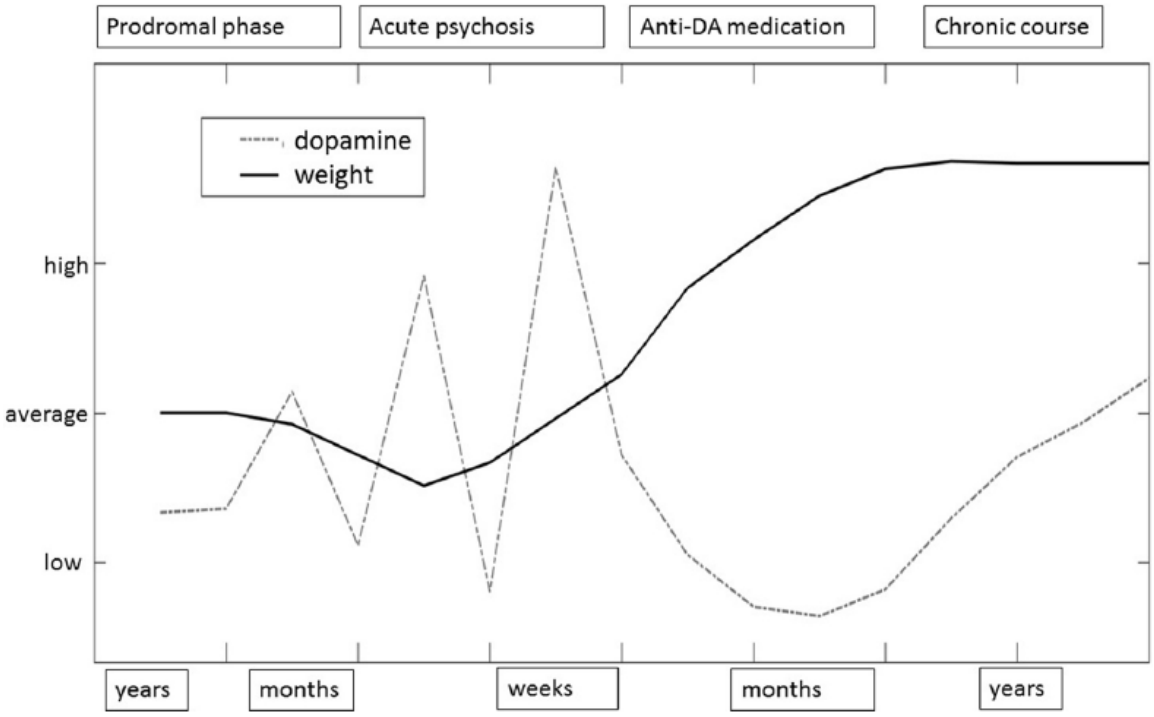
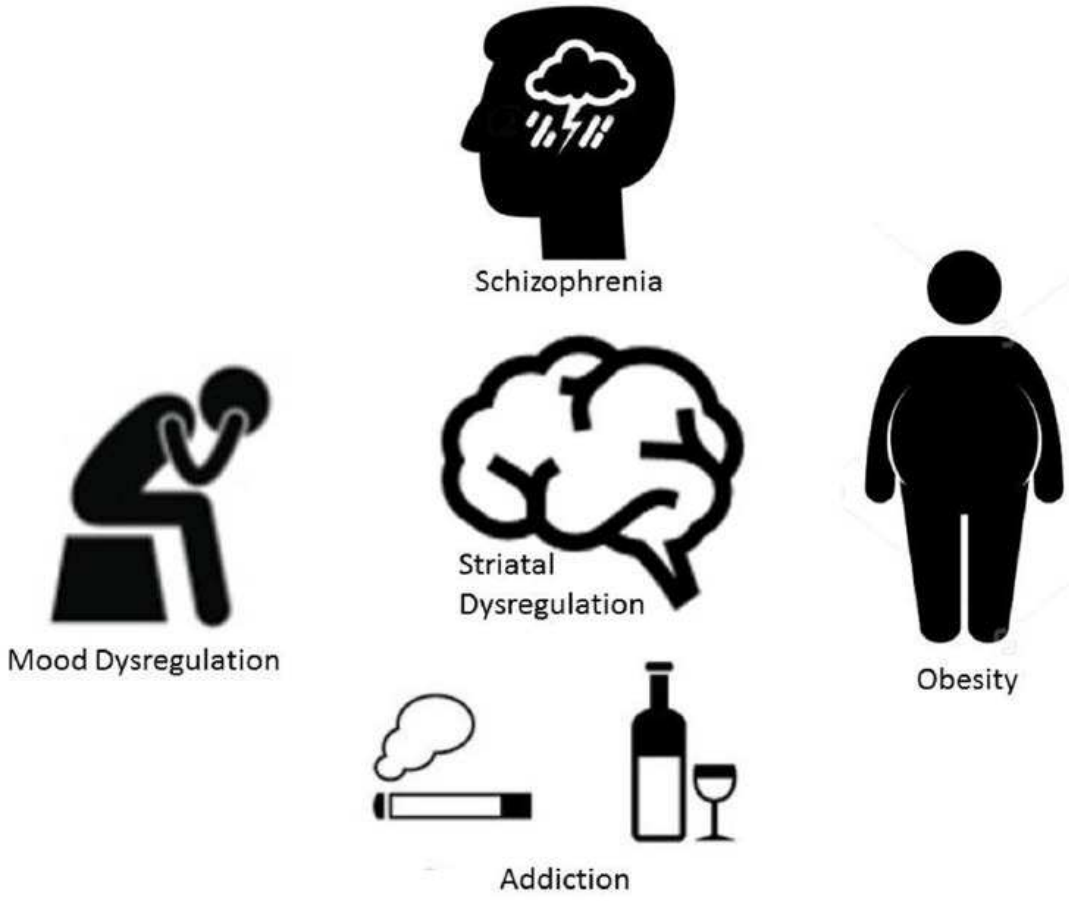

Prodromal phase
Acute psychosis
Anti-DA medication
Chronic course
dopamine
weight
high
average
low
years
months
weeks
months
years

Figure 2.


Schizophrenia
Striatal
Dysregulation
Mood Dysregulation
Obesity
Addiction